factor-alpha neutralizing antibody or pretreatment with cyclophosphamide abolished plug-induced EGFR protein expression and *goblet* *cell* *metaplasia*. Thus instillation of agarose plugs induces profound *goblet* *cell* *metaplasia* by causing EGFR expression and activation.

5/3,K/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11971290 BIOSIS NO.: 199900224603
Epidermal growth factor system regulates mucin production in airways.
AUTHOR: Takeyama Kiyoshi; Dabbagh Karim; Lee Heung-Man; Agusti Carlos; Lausier James A; Ueki Iris F; Grattan Kathleen M; Nadel Jay A(a)
AUTHOR ADDRESS: (a)Cardiovascular Research Institute, University of California, San Francisco, CA, 94143-0130**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 96 (6):p3081-3086 March 16, 1999
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: *Goblet*-*cell* hyperplasia is a critical pathological feature in hypersecretory diseases of airways. However, the underlying mechanisms are unknown, and no effective therapy exists. Here we show that stimulation of epidermal *growth* factor receptors (EGF-R) by its ligands, EGF and transforming *growth* factor alpha (TGFalpha), causes MUC5AC expression in airway epithelial cells both in in vitro and in vivo. We found that a MUC5AC-inducing epithelial cell...
...TNFalpha). EGF-R ligands increased the expression of MUC5AC at both gene and protein levels, and this effect was potentiated by TNFalpha. Selective EGF-R *tyrosine* *kinase* *inhibitors* blocked MUC5AC expression induced by EGF-R ligands. Pathogen-free rats expressed little EGF-R protein in airway epithelial cells; intratracheal instillation of TNFalpha induced EGF-R in airway epithelial cells, and subsequent instillation of EGF-R ligands increased the number of *goblet* *cells*, Alcian blue-periodic acid-Schiff staining (reflecting mucous glycoconjugates), and MUC5AC gene expression, whereas TNFalpha, EGF, or TGFalpha alone was without effect. In sensitized rats, three intratracheal instillations of ovalbumin resulted in EGF-R expression and *goblet*-*cell* production in airway epithelium. Pretreatment with EGF-R *tyrosine* *kinase* *inhibitor*, BIBX1522, prevented *goblet*-*cell* production both in rats stimulated by TNFalpha-EGF-R ligands and in an asthma model. These findings suggest potential roles for inhibitors of the EGF...

5/3,K/7 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

15020222 PASCAL No.: 01-0176799
IL-13 induces mucin production by stimulating epidermal growth factor receptors and by activating neutrophils
JAE JEONG SHIM; DABBAGH Karim; UEKI Iris F; DAO-PICK Trang; BURGEL Pierre-Regis; TAKEYAMA Kiyoshi; TAM Dominic Cheng-Wei; NADEL Jay A
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Journal: American journal of physiology. Lung cellular and molecular physiology, 2001, 24 (1) L134-L140
Language: English

Mucus hypersecretion contributes to the morbidity and mortality in acute

asthma. Both T helper 2 (Th2) cytokines and epidermal *growth* factor receptor (EGFR) signaling have been implicated in allergen-induced *goblet* *cell* (GC) *metaplasia* . Present results show that a cascade of EGFR involving neutrophils is implicated in interleukin (IL)-13-induced mucin expression in GC. Treatment with a selective EGFR *tyrosine* *kinase* *inhibitor* prevented IL-13-induced GC *metaplasia* dose dependently and completely. Instillation of IL-13 also induced tumor necrosis factor-a protein expression, mainly in infiltrating neutrophils. Control airway epithelium contained few...

... inhibitor of leukocytes in the bone marrow (cyclophosphamide) or with a blocking antibody to IL-8 prevented both IL-13-induced leukocyte recruitment and GC *metaplasia* . These findings indicate that EGFR signaling is involved in IL-13-induced mucin production. They suggest a potential therapeutic role for inhibitors of the EGFR...

5/3,K/8 (Item 1 from file: 149)

01912074 SUPPLIER NUMBER: 62495087 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Mechanisms of Airway Hypersecretion and Novel Therapy(*).
Nadel, Jay A.
Chest, 117, 5, 262S
May,
2000
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0012-3692
LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3503 LINE COUNT: 00304

... have focused the present studies on the mechanism of goblet cell formation (rather than degranulation).

We hypothesized that a growth factor could be involved in *goblet* *cell* production, because hypersecretory diseases are associated with abnormal epithelial *growth* and *proliferation*. A possible candidate is epidermal *growth* factor (EGF) and its receptor EGF-R. EGF-R, a 70-kd membrane glycoprotein, is expressed in fetal airways, where it is important in cell *proliferation*, branching morphogenesis, and epithelial cell differentiation.(9) In healthy adult human airways, expression of EGF-R is sparse, but EGF-R is expressed in malignant...
...by tumor necrosis factor (TNF)-(Alpha) in lungs in hypersecretory diseases.(11) Therefore, we hypothesized that the EGF-R system could play a role in *goblet* *cell* production in disease. We found that stimulation of airway epithelial cells with TNF-(Alpha) induces EGF-R in epithelial cell cultures and in rats in vivo.(8) Further, we showed that stimulation of EGF-R by its ligands results in mucus-producing *goblet* *cells*, and that ovalbumin (OVA) sensitization in rats causes induction of EGF-R and *goblet* *cell* production in rat airways. A key discovery is that selective EGF-R *tyrosine* *kinase* *inhibitors* prevent mucus production in each of these systems. We suggest that inhibitors of EGF-R could be useful in preventing *goblet* *cell* production and thus hypersecretion in disease. The studies are reported in detail elsewhere.(8) Only the in vivo studies are reported here.

MATERIALS AND METHODS...by instillation of OVA into the airways resulted in the expression of EGF-R in the epithelium and the conversion of epithelial cells to the *goblet* *cell* phenotype. Most interestingly, a selective *inhibitor* of EGF-R *tyrosine* *kinase* completely *inhibited* *goblet* *cell* production in rats stimulated with TNF-(Alpha) plus an EGF-R ligand or sensitized with OVA. These results incriminate EGF-R activation in *goblet* *cell* *metaplasia*.

Previous studies showed that various stimuli such as ozone,(15) sulfur dioxide,(16) viruses,(16) lipopolysaccharide(15,17) and platelet-activating factor(12) up-regulate...

...is described elsewhere.(14)

In summary, the EGF-R cascade is shown by the present studies to be important in stimulating the growth of airway *goblet* *cells*, which are

implicated in mucus hypersecretion, especially in peripheral airways where lesions are difficult to detect and potentially lethal. Treatment with selective *inhibitors* of EGF-R *tyrosine* *kinase* may provide effective therapy in hypersecretory diseases of airways.

REFERENCES

(1) Snider GL, Faling LJ, Rennard SI. Chronic bronchitis and emphysema. In: Murray JF, Nadel...

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